Office of: Jenny L. Peters
Global Regulatory Intelligence
Mailstop 0636-298-112

Telephone No. (616) 833-8141
Facsimile No. (616) 833-0409

October 21, 1999

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket 99D-2729
BA and BE Studies for Orally Administered
Drug Products - General Considerations

Dear Sir/Madam,

As a company actively engaged in the drug development process, Pharmacia and Upjohn appreciates FDA's issuance of the draft guidance for industry, "BA and BE Studies for Orally Administered Drug Products - General Considerations" (September 3, 1999, FEDERAL REGISTER, pages 48409-48410). Our comments on this guidance are outlined below.

1. III.A.5. Study Population
   Given the relatively small sample size associated with bioavailability (BA) and bioequivalence (BE) studies, it will be difficult to recruit a truly heterogeneous study population. With regard to data analysis, the number of subjects in any given subgroup may be quite small, allowing only for inferences on potential subgroup by formulation interactions. Furthermore, balance within randomization groups is also an issue. If there are concerns regarding an effect of race, gender, age, etc on drug bioavailability, it would be better to do separate studies or pool data from several studies. There will be insufficient power to test subgroup by formulation interactions within the framework of a BA/BE study.

99D-2729

C1

2. III.A.8a. Early Exposure
Measurement of the partial area under the concentration-time profile curve with a cutoff at the peak time of the reference formulation in each subject is computationally burdensome. The rationale for selection of this metric is not provided in this guidance. In a paper by Lacey et al (J Pharm Sci 1994;2:212-215), it was shown that $C_{max}/AUC_{0-\infty}$ is the most sensitive and powerful indirect measure of rate of drug absorption in comparative studies involving immediate-release dosage forms. The partial AUC, as defined in the guidance, was demonstrated to be imprecisely estimated and of no practical value as a measure of rate of absorption. In another paper (Pharm Res 1994; 11:831-4), Macheras et al. reported that a partial AUC to t_{max} of the more rapidly absorbed formulation was the most practical cutoff time point, but only for drugs with one-compartment model disposition and linear absorption. Additional limitations are factors which affect the ability to define t_{max}, such as the frequency of sampling in the region of the peak and variable lag times in conjunction with the limit of quantitation of the assay. Therefore, consideration should be given to use of $C_{max}/AUC_{0-\infty}$, which is likely a more robust metric than partial AUC to t_{max}.

3. III.A.8c. Total Exposure
The extrapolation to infinity of the AUC_{0-T} involves use of C_t, the last measurable drug concentration. Because of the greater error associated with measurement of concentrations in this region of the concentration-time curve, it is preferable to use the extrapolated C_t which is based on the calculated λ_z. The guidance should allow for either the measured or extrapolated C_t to be employed in this calculation.

4. IV. Comparison of BA Measures in BE Studies
The draft guidance states that sponsors may analyze their data using either average or population BE criteria for INDs and NDAs and average or individual BE criteria for NDAs and ANDAs, provided the choice is specified in the study protocol prior to study initiation. For BE studies, we feel that the same statistical criteria should be used by all sponsors, and this should be the ABE methodology.

5. V.C.1. General Recommendations
For drugs with a narrow therapeutic range, it is proposed that the ABE limits be tightened. Most drugs in this category are subject to therapeutic drug monitoring; therefore, these stricter BE limits would not appear to be necessary. In the last sentence, the terms epsilon and theta are not defined. Reference should be made directly to the guidance which contains the details for calculating allowable upper limits.

6. V.D.2. ANDAs: BE Studies
The tighter ABE limits for drugs that exhibit nonlinear kinetics and are safe over a wide therapeutic range would appear to be overly stringent. Consideration should be given to excluding such drugs from this requirement.

7. V.E. Miscellaneous Dosage Forms
   We do not understand the rationale for testing chewable tablets under the same in vitro dissolution conditions as non-chewable tablets of the same active moiety. While we agree that an in vitro dissolution test is important as a quality control tool, any differences in the dissolution profiles would be inconclusive with respect to bioavailability unless an in vitro–in vivo correlation had been established for the non-chewable tablet. Additionally, industry should not be obligated to test the performance of a product under conditions of non-compliant use, i.e. swallowing chewable tablets without proper chewing.

8. Appendix 2, Study conduct
   In the 4th bullet point, it should be clarified that drug content refers to "labeled" content.

9. Appendix 2, Pharmacokinetic information recommended for submission
   Statistical information on several parameters of questionable utility is suggested, such as $AUC_{0-t}/AUC_{0-\infty}$. Also, the wording in this sentence would imply that confidence intervals for arithmetic means of all the stated parameters are necessary. This sentence should be reworded to state that all the suggested metrics are necessary only for AUC and C_{max} and the rest can be included as appropriate.

10. Appendix 2, Rounding off of confidence interval values
    The stipulation to not allow for rounding of confidence interval values is likely due to repeated liberal interpretations of values falling near the specified limits for BE. It would seem reasonable to state that numerical rounding would be allowed for values greater than 79.49 and less than 125.50 rather than the proposed, overly stringent procedure.

We thank you for the opportunity to comment on this draft. Please let us know if you have any questions on our review.

Sincerely,

Pharmacia & Upjohn Company

Jenny Peters
(616)-833-8141
Director
Global Regulatory Intelligence

FROM

[redacted] PHARMACIA & UPJOHN INC
[redacted] 295 0636-295-111
[redacted] PORTAGE RD
[redacted] MI [redacted]
[redacted] Peters (616) 833-8141

TO

[redacted] and Drug Administration
[redacted] Fishers Lane, Room 1061
[redacted]ville MD 20852
Dockets Management Branch (HFA-305)

* 7 0 2 1 8 8 8 7 2 0 *

001 (9.98) S-06
PACKAGE LABEL

Preprint Format No. | Origin | Airbill Number 7021888720

Method of Payment — Assumed sender unless otherwise noted

- ☐ Bill Sender
- ☐ Bill Receiver
- ☐ Bill 3rd Party
- ☐ Paid in Advance

AIRBORNE EXPRESS.

EXP (Letter - 150 lbs)

NAS (Letter - 5 lbs)

SDS (Letter - 150 lbs)

Billing Reference *will appear on invoice*

[redacted]

NO. of Pkgs.	Weight (LBS)	One box **must** be checked: Letter Express	Express Pack	Other Packaging
1	1#		X	

Special Instructions

☐ SAT ☐ HAA

☐ LAB ☐

MLDA24X